ORIGINAL CONTRIBUTION

Change in Cognitive Function Over Time in Very Low-Birth-Weight Infants

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Context Preterm very low-birth-weight (VLBW) infants have a high prevalence of neurodevelopmental disability when evaluated during the first several years of life. However, recent experimental data suggest that the developing brain may recover from or compensate for injury.

Objective To determine if there is cognitive improvement throughout early and middle childhood following VLBW birth.

Design, Setting, and Participants Follow-up data of 296 infants born weighing 600 to 1250 g who participated in a prospective, randomized, placebo-controlled intraventricular hemorrhage (IVH) prevention study performed at 3 northeastern US hospitals between September 1989 and August 1992 and who were serially evaluated at 36, 54, 72, and 96 months of corrected age (CA).

Main Outcome Measures The age-normed Peabody Picture Vocabulary Test–Revised (PPVT-R) score and measures of intelligence.

Results Overall, the median PPVT-R score increased from 88 at 36 months of CA to 99 at 96 months of CA; when data from 36 and 96 months of CA were compared, 45% of children gained 10 points or more and 12.5% showed a 5- to 9-point increase in test scores. Similar findings were noted for full-scale and verbal IQ scores. Multivariate analyses demonstrated that increasing age, residence in a 2-parent household, and higher levels of maternal education were all significantly associated with higher PPVT-R scores (for each, $P<.001$). In addition, early intervention led to greater increases over time in PPVT-R scores among children whose mothers had less than a high school education compared with those with a high school education level or greater ($P=.03$ by test for interaction). Although most children showed improvement in PPVT-R scores with increasing CA, children with early-onset IVH and subsequent significant central nervous system injury had the lowest PPVT-R scores initially and the scores declined over time ($P=.009$ by test for interaction).

Conclusions The majority of VLBW children had improvement in verbal and IQ test scores over time. Only children with early-onset IVH followed by significant central nervous system injury had low PPVT-R scores that declined over time.

JAMA. 2003;289:705-711 www.jama.com

PRETERM BIRTH RESULTS IN SIGnificant neurodevelopmental disability during childhood.[1,2] Depending on the birth weight of the children studied and the years in which they were born, the incidence of major disabilities ranges from 20% to almost 50% in the first several years of life.[3-8] In addition, almost one fifth develop major cognitive disabilities by age 8 years,[9,10] more than 50% are reported to require special assistance in the classroom, 20% are in special education, and 15% have repeated at least 1 grade in elementary school.[10-13] However, recent reports suggest that two thirds of preterm infants require no special assistance in school at ages 14 to 15 years, almost three quarters graduate from high school, and more than 40% are enrolled in college programs. These data suggest change in cognitive function over time in those born preterm.[14-18]

Survivors in the multicenter Randomized Indomethacin Intraventricular Hemorrhage (IVH) Prevention Trial were studied to test the hypothesis that verbal and cognitive performance of very low-birth-weight (VLBW) infants would improve relative to an age-standardized group throughout early and middle childhood.[19-23] Serial measures of cognitive and verbal skills were performed and the effects of time and previously described biological and environmental risk factors were assessed.

See also p 752 and Patient Page.

METHODS

The Randomized Indomethacin IVH Prevention Trial was conducted at Women and Infants' Hospital, Providence, RI; Maine Medical Center, Portland; and Yale New Haven Hospital, New Haven, Conn. The protocols were reviewed and approved by the institutional review boards of each institution. Informed consent was obtained from all parents and children.

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Between September 5, 1989, and August 31, 1992, 505 infants weighing 600 to 1250 g at birth were admitted within 6 hours of birth to 2 parallel randomized, prospective, low-dose indomethacin IVH prevention trials.[19,20] All infants were examined using cranial echoencephalography (ECHO) between 5 and 11 hours after birth. Of the 505 enrolled infants, 431 had normal ECHO studies and were considered early IVH negative. Seventy-four infants had ECHO evidence for IVH at this time; these were called early IVH positive.

Subsequent scans were performed 24 and 48 hours after the first scan; 4, 5, 7, 14, and 21 days after birth; and at 40 weeks' postmenstrual age. Scans were interpreted by the institutional radiologist and independently verified by a central radiologist. In cases of disagreement, data were reexamined by all participating radiologists and a consensus was reached.

Radiologic assessment was performed without prior knowledge of the infant's clinical condition. The grading system for hemorrhages was as follows[19,20]: grade 1 (blood in the germinal matrix regions); grade 2 (blood within the lateral ventricular system without ventricular dilation); grade 3 (blood within and distending the lateral ventricles); and grade 4 (blood within the ventricular system and parenchymal involvement). Ventriculomegaly was assessed at 40 weeks' postmenstrual age (or if not available 21 days after birth). Moderate and severe ventriculomegaly were defined as measurements of 1.0 to 1.5 cm and more than 1.5 cm, respectively, at the midbody of the lateral ventricle on sagittal scan.[24] Studies were also evaluated for focal echolucencies. All cases showing focal echolucencies had cystic areas consistent with periventricular leukomalacia (PVL) on the ultrasound performed at 40 weeks' postmenstrual age.[24] A study infant was defined as having significant central nervous system (CNS) injury if he/she had 1 or more of the following 3 ultrasound findings: grade 4 IVH at any time following the first scan at 5 to 11 hours; PVL at term; or ventriculomegaly at term. No study infant had grade 4 IVH at 6 postnatal hours.

All infants underwent gestational age assessment using a modification of the Ballard scale.[25] Prenatal, perinatal, and neonatal data were obtained by maternal interviews and review of the maternal and neonatal charts. Resuscitation scores were as follows: 0, no intervention; 1, blow-by oxygen, tactile stimulation, or both; 2, endotracheal suctioning only; 3, bag-and-mask positive-pressure ventilation; 4, endotracheal intubation and positive-pressure ventilation; and 5, endotracheal intubation, positive-pressure ventilation, and the use of drugs, cardiac massage, or both. Randomization to low-dose indomethacin was categorized as present/absent. An infant was diagnosed with bronchopulmonary dysplasia (BPD) if he/she both required oxygen supplementation and had an abnormal chest radiograph at 28 days of life[26]; BPD was categorized as present/absent.

Neurodevelopmental Assessments

Serial neurodevelopmental follow-up evaluations were performed on all study participants. At 36 months of corrected age (CA, ie, months past the obstetric due date), each child was tested with the Peabody Picture Vocabulary Test–Revised (PPVT-R),[27] an age-normed test that requires no verbal responses from the child and measures receptive vocabulary words of individuals aged 2½ years through adulthood. Raw scores are converted to standard scores with a mean (SD) of 100 (15) points. The PPVT-R does not require a motor response and is thus an excellent instrument for use with children with motor disabilities.[28] Study children also were evaluated at 36 months with the Stanford-Binet Intelligence Scale (SBIS, Form L-M), which produces standardized scores with a mean (SD) of 100 (16) points.[29]

At both 54 and 72 months of CA, each child was tested with the PPVT-R and the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI-R).[30] The WPPSI-R is an individually administered, norm-referenced instrument for assessing the intellectual functioning of children aged 3 years 0 months through 7 years 3 months and provides 3 intelligence scores: a performance IQ (PIQ), verbal IQ (VIQ), and full-scale IQ. All 3 scores have a mean (SD) of 100 (15).

At 96 months of CA, children were evaluated with the PPVT-R and the Wechsler Intelligence Scale for Children–Third Edition (WISC-III),[31] a norm-referenced instrument for assessing the intellectual function of children aged 6 years 0 months through 16 years 11 months. The WISC-III also provides 3 IQ scores: PIQ, VIQ, and full-scale IQ, with a mean (SD) of 100 (15).

The full battery of tests was administered to all children. Some demonstrated significant impairments, resulting in raw scores of 0 for some of the tests. When raw scores on the PPVT-R fall below the lowest score for which a standard score can be computed, the PPVT-R manual assigns a score of less than 20 for the score.[27] In our statistical analyses, the earned score of less than 20 was converted to a score of 19. Similarly, if a basal score was unable to be calculated for any of the IQ assessments, a score of 1 point less than the lowest score for the test for the overall population was assigned to that child (ie, 33 for the SBIS, 40 for the WPPSI-R full-scale IQ, 45 for the WPPSI-R VIQ, and 44 for the WPPSI-R PIQ).[31] Only 1 child, who was early IVH negative, was found to have values of 19 for all PPVT-R tests; the same child received lowest values for IQ tests at all 4 time evaluations.

Neurological examinations were performed at each follow-up assessment.[24] Assignment of the diagnosis of cerebral palsy was based on the presence of hypertonicity, hyperreflexia, and dystonic or spastic movements in the affected extremities. Whether the child received blind services was collected from parent/caregiver report and was coded yes/no. None of the 7 children receiving blind services received scores of 19 for any PPVT-R test. Deaf children were defined as those requiring amplification bilaterally.

Prior to each evaluation time, all neurodevelopmental testers were certified for the study outcome measures on 4

nonstudy age-appropriate participants by the study's psychologist. Assessors were recertified annually on 2 nonstudy age-appropriate children. Teams that performed the neurodevelopmental examinations remained blinded with regard to the participants' current and previous medical histories.

Demographic Data

Demographic information was obtained from the primary caregivers. Maternal education was categorized as less than high school or high school graduate or higher. Residence in a 2-parent household at 96 months of CA was coded yes/no, and parents were defined as birth mother, adoptive mother, stepmother, and/or birth father, adoptive father, and stepfather. Early intervention services including occupational therapy, physical therapy, speech, and/or language therapy were obtained from parent/caregiver report. A child was considered positive for these special services if he/she received 1 or more services at 36 months of CA, consistent with previous studies.[13,32]

Statistical Methods

Because those children with early-onset IVH are at the highest risk for disability in childhood,[33] study participants were divided into early IVH negative and early IVH positive groups to evaluate scores across ages. The PPVT-R scores were selected as our primary outcome measure prior to statistical analysis, because the same test was used at all 4 measurements. The IQ scores were a secondary outcome measure. Finally, z scores were calculated for the full-scale IQ, VIQ, and PIQ scores for each child at each age.

To understand important biological or environmental factors that may be associated with testing scores, factors reported to be associated with neurodevelopmental outcome in VLBW infants[11,13,15,22,32,34,35] were evaluated: birth weight of 750 g or less, male sex, randomization to indomethacin, BPD, evidence for significant CNS injury in the neonatal period, non-English monolingual or bilingual household (language), maternal education, residence in a 2-parent household, and the use of special services at 36 months of CA.

Categorical data with no expectation of a linear trend among groups (eg, sex) were analyzed using Fisher exact test. Categorical data with an a priori expectation of a linear trend among groups were analyzed by the χ^2 test for linear trend. The 2-sample Wilcoxon rank sum test was used for between-group comparisons of continuous data. Because PPVT-R scores were not always normally distributed, summary statistics for this factor were reported using medians and ranges.

Hierarchical multivariate regression models were used to examine the effect of several factors simultaneously. All significant higher-order interaction terms required inclusion of all lower order (ie, main effect) factors in the model. The first model evaluated the main effects only to determine which factors played an independent role in predicting PPVT-R scores. Using this reduced set of important factors, a second model was developed in which the main effects and the interaction of these factors with one another were explored. A significant interaction implies that the effect of one factor on PPVT-R scores varies significantly according to the level of the other factor. All statistical analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC). All P values are 2-sided and statistical significance was assigned at $P<.05$.

RESULTS

Description of the Study Population

At 36 months of CA, there were 440 survivors of the original 505 study participants (87%). Of the 440, 385 (88%) were observed for at least 1 assessment, 363 (82.5%) were evaluated at 36 months of CA, 359 (81.5%) were observed at 54 months of CA, and 358 (81%) and 368 (84%) were evaluated at 72 and 96 months of CA, respectively. A total of 296 children (67%) underwent serial PPVT-R testing at all 4 evaluations.

TABLE 1 summarizes baseline and demographic characteristics of all participants at the 4 evaluations and the subgroup with measurements at all assessment times. Because these data showed no difference for any of the variables among the groups of children, we describe results for the 296 children observed for all 4 evaluations.

Comparing the 261 early IVH negative and 35 early IVH positive children demonstrated no marked differences for birth weight, incidence of birth weight of 750 g or less, gestational age, male sex, maternal education, antenatal steroid exposure, 1-minute Apgar scores, resuscitation scores, or BPD between the 2 groups. The median (range) 5-minute Apgar score for children who were early IVH negative was 7 (1-9); for children who were early IVH positive, it was 6 (1-9; $P=.03$). The early IVH positive group had a higher percentage of ventriculomegaly (6 [2%] vs 6 [17%]; $P=.001$) and grade 4 IVH compared with the early IVH negative group (5 [2%] vs 3 [9%]; $P<.001$) with a trend for more PVL (9 [3.5%] vs 4 [11%]; $P=.06$). Eight children who were early IVH positive (23%) had 1 or more of these 3 adverse outcomes compared with 16 children who were early IVH negative (6%, $P<.001$).

At 36 months of CA, 68 early IVH negative (26%) and 15 early IVH positive (43%) children were receiving special services ($P=.03$). Fifteen of the 24 children (62.5%) with significant CNS injury were receiving special services compared with 63 children (25%) without significant CNS injury ($P<.001$). Sixty-five early IVH negative (25%) and 16 early IVH positive (46%) participants were living in households in which English was not the primary language ($P=.01$).

Twenty-two of the 258 early IVH negative children (9%) with neurological examinations and 6 early IVH positive children (17%) had cerebral palsy ($P=.12$). Similarly, 4 early IVH negative children (2%) and 3 early IVH positive children (9%) were receiving blind services at age 8 years ($P=.04$); 6 (3 negative and 3 positive) had a history of retinopathy of prematurity, although 1 early IVH negative child had a stroke in-

Table 1. Baseline and Demographic Characteristics of the Population

Characteristic	Corrected Age, mo				
	36 (n = 363)	54 (n = 359)	72 (n = 358)	96 (n = 368)	All 4 (n = 296)
Birth weight, mean (SD), g	960 (173)	962 (176)	960 (173)	962 (175)	965 (174)
Gestational age, mean (SD), wk	28.0 (2.0)	28.0 (2.0)	28.0 (2.0)	28.0 (2.0)	28.0 (2.0)
Sex, male, No. (%)	196 (54)	195 (54)	188 (53)	197 (54)	156 (53)
Maternal age, mean (SD), y	27.7 (6.0)	27.7 (6.3)	27.6 (6.2)	27.6 (6.1)	28.0 (6.2)
Maternal education, mean (SD), y	13.1 (2.2)	13.2 (2.2)	13.1 (2.2)	13.1 (2.1)	13.2 (2.2)
Antenatal corticosteroid exposure, No. (%)	125 (34)	124 (35)	124 (35)	124 (34)	109 (37)
Resuscitation score, median (range)	4 (0-5)	4 (0-5)	4 (0-5)	4 (0-5)	4 (0-5)
Apgar score at 1 min, median (range)	5 (0-9)	5 (0-9)	5 (0-9)	5 (0-9)	5 (0-9)
Apgar score at 5 min, median (range)	7 (1-9)	7 (1-9)	7 (1-9)	7 (1-9)	7 (1-9)
Early IVH positive, No. (%)	45 (12)	45 (13)	44 (12)	46 (13)	35 (12)
Periventricular leukomalacia, No. (%)	15 (4)	14 (4)	14 (4)	15 (4)	13 (4)
Ventriculomegaly, No. (%)	17 (5)	16 (5)	19 (5)	20 (5)	12 (4)
Grade 4 IVH, No. (%)	13 (3.6)	11 (3.1)	12 (3.4)	13 (3.5)	8 (3)
Bronchopulmonary dysplasia, No. (%)	168 (46)	166 (46)	163 (46)	164 (45)	134 (45)

Abbreviation: IVH, intraventricular hemorrhage.

Table 2. Serial Peabody Picture Vocabulary Test–Revised Scores With Increasing Corrected Ages

	Median (Range) Scores for Corrected Age, mo			
	36	54	72	96
IVH negative (n = 261)	89 (20-135)	92 (19-142)	97 (19-142)	99 (19-153)
IVH positive (n = 35)	85 (33-120)	90 (19-120)	96 (19-128)	96 (19-139)

Abbreviation: IVH, intraventricular hemorrhage.

volving the periventricular white matter. The incidence of deafness was 3% in both groups. A total of 213 children (185 early IVH negative [71%] and 28 early IVH positive [80%]; $P=.26$) were living in 2-parent households.

Serial PPVT-R Scores

Overall, the median (range) PPVT-R scores were 88.0 (20-135), 91.0 (19-142), 97.0 (19-142), and 99.0 (19-153) at 36, 54, 72, and 96 months of CA, respectively. Scores for the 25th percentile were 74.2, 74.7, 82.5, and 83.5 for 36, 54, 72, and 96 months of CA, respectively; those for the 75th percentile were 100.2, 101.3, 110.2, and 109.5, respectively. Comparison of the scores at 36 and 96 months of CA for all children showed a significant effect of time ($P<.001$, Wilcoxon signed rank test). A total of 134 children (45%) had increases in scores of 10 points or more, 37 (12.5%) had increases of 5 to 9 points, 27 (9%) had either no increase or an increase of 0 to 4 points, 30 (10%) had decreases of 1 to 4 points, 19 (6%) had decreases of 5 to 9 points, and 49 (17%) had decreases of 10 points or more. Furthermore, 35 of 49 children (71%) with scores in the borderline range (70-80) at 36 months were found to have scores in the normal range (>80) at 96 months and 28 of 57 children (49%) with scores less than 70 at 36 months no longer had scores in the mental retardation range (<70) at 96 months of CA.

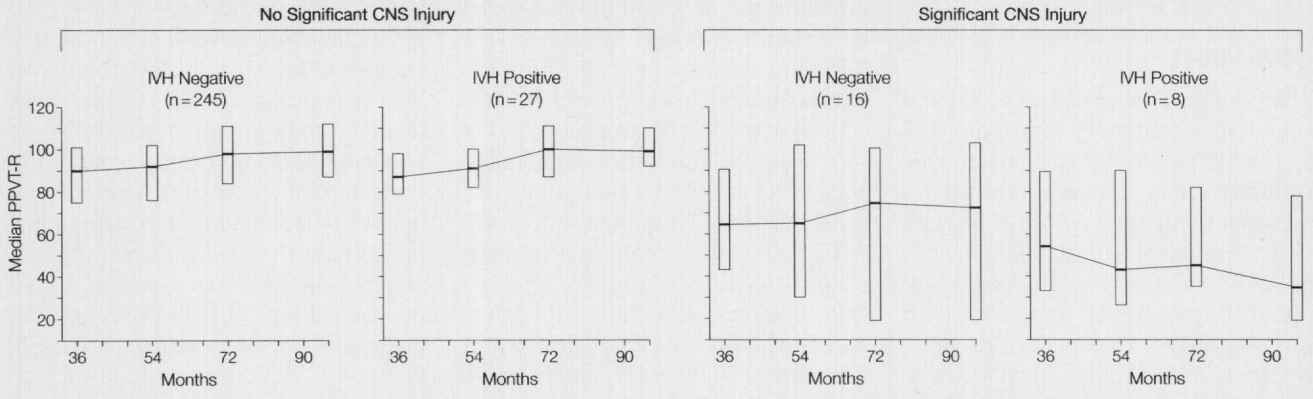
The median PPVT-R scores for the early IVH negative group were higher at all 4 evaluations compared with the early IVH positive group (TABLE 2). Both groups show a similar trend for higher scores with increasing CA. A multivariate regression analysis shows PPVT-R scores are higher with increasing CA ($P<.001$), and a possible trend may exist for these scores to differ between early IVH negative and positive participants ($P=.09$).

Multivariate Analysis of Risk Factors on PPVT-R Scores

Given the evidence for higher scores with increasing age, we examined a variety of biological and environmental factors to determine the nature and extent of their contribution. In a multivariate model, which included main effects only, a birth weight of 750 g or less, male sex, randomization to early low-dose indomethacin, early IVH positive vs early IVH negative, BPD, and language each were not significantly associated with PPVT-R scores in the presence of group and time ($P=.89$, .51, .64, .72, .65, and .11, respectively). However, increasing CA, higher levels of maternal education, residence in a 2-parent household, absence of special services, and absence of significant CNS injury all were significantly associated with higher PPVT-R scores ($P<.001$ for all).

Statistically significant factors were selected for further evaluation of interaction between factors. Early IVH status was retained in the model to determine its importance in the presence of these factors. The PPVT-R scores changed with increasing CA in a markedly different way according to the presence of significant CNS injury ($P=.009$, test for interaction) (FIGURE). Participants who were early IVH negative and did not suffer significant CNS injury had the highest PPVT-R scores; they are similar to the early IVH positive children without significant CNS injury. Participants who were early IVH negative with significant CNS injury had smaller increases

Figure. Serial Peabody Picture Vocabulary Test–Revised (PPVT-R) Scores With Increasing Corrected Ages



Median scores with interquartile ranges for 245 early intraventricular hemorrhage (IVH) negative children with no evidence for significant central nervous system (CNS) injury, 16 early IVH negative children with significant CNS injury, 27 early IVH positive children without injury, and 8 early IVH positive children with injury. Multivariate analysis shows a significant age × significant CNS injury interaction ($P=.009$).

over time on the PPVT-R scores than the first 2 groups. Finally, the participants who were early IVH positive and had significant CNS injury had the lowest PPVT-R scores. Moreover, in contrast with the higher scores with increasing CA in PPVT-R scores for the other groups, these children had lower scores with increasing CA.

The extent of higher PPVT-R scores observed over time also differed according to the presence of a 2-parent household. Children residing in a 2-parent household had a greater improvement in scores over time compared with those children not residing in a 2-parent household ($P=.04$, test for interaction). Among the children of mothers with less than a high school education, the use of special services was associated with a greater increase in PPVT-R scores ($P=.03$, test for interaction).

Table 3. Serial IQ Scores With Increasing Corrected Ages*

	Median (Range) Scores for Corrected Age, mo			
	36	54	72	96
IVH negative				
Full-scale IQ	90 (33-134)	90 (40-129)	93 (40-140)	96 (40-129)
Verbal IQ	NA	91.5 (45-135)	94 (45-148)	98 (46-142)
Performance IQ	NA	90 (44-126)	91 (44-130)	94 (46-139)
IVH positive				
Full-scale IQ	88 (43-118)	89 (40-133)	90.5 (40-156)	94 (40-139)
Verbal IQ	NA	91 (45-131)	92 (45-132)	97 (46-140)
Performance IQ	NA	89 (44-120)	87.5 (44-143)	91 (46-131)

Abbreviations: IVH, intraventricular hemorrhage; NA, not applicable.
*At 36 months of corrected age, Stanford-Binet Intelligence Scale was used; at 54 and 72 months of corrected age, Wechsler Preschool and Primary Scale of Intelligence–Revised was used; and at 96 months of corrected age, Wechsler Intelligence Scale for Children–Third Edition was used.

Serial IQ Scores

The overall median (range) full-scale IQ scores for the children were 90.0 (33-134), 90.0 (40-133), 93.0 (40-156), and 95.0 (40-139) at 36, 54, 72, and 96 months of CA, respectively. The VIQ scores were 91.0 (45-135), 94.0 (45-151), and 97.5 (46-142) at 54, 72, and 96 months of CA, respectively. The PIQ scores for the same 3 evaluations were 89.0 (44-126), 91 (44-143), and 92 (46-139), respectively.

The per-group serial IQ scores for the early IVH negative and early IVH positive children evaluated at each age are shown in TABLE 3. A multivariate regression analysis shows significantly higher full-scale IQ scores ($P=.008$) and VIQ scores ($P<.001$) with increasing CA. A marginal trend was also observed in PIQ scores ($P=.11$). There were no group effects in any of the models; the effect was similar in the early IVH positive and early IVH negative groups.

When the per-group serial IQ scores are evaluated as z scores, the multivariate regression analysis shows significantly higher full-scale IQ scores over time ($P=.004$), but no marked difference exists between the early IVH negative and early IVH positive groups ($P=.21$). The VIQ z scores also were significantly higher with increasing CA ($P<.001$), with no marked difference between groups ($P=.27$). A marginal trend was observed for higher PIQ z scores with increasing CA ($P=.11$), with no marked difference between groups ($P=.23$).

The VIQ z scores were analyzed using the same multivariate model reported for PPVT-R scores. With increasing CA, higher levels of maternal education ($P<.001$), residence in a 2-parent household ($P=.002$), absence of special services ($P<.001$), and absence of significant CNS injury ($P<.001$) were all significantly associated with higher VIQ scores. Among the children of mothers with less than a high school education, the use of special services was associated with a

greater increase in VIQ z scores compared with absence of special service use ($P=.005$, test for interaction).

COMMENT

This longitudinal study of verbal and cognitive function of a large cohort of VLBW infants through early and middle childhood demonstrates continued improvement in both PPVT-R and IQ scores compared with standard norms. Both children with no evidence for cerebral injury at birth and those with early-onset IVH experienced progressive increases in scores when tested at 36, 54, 72, and 96 months of CA. However, those children with IVH at 5 to 11 postnatal hours and significant CNS injury thereafter showed a decline in PPVT-R scores. Although we report data for the 296 children who were seen at all 4 evaluations, we obtained similar results (using mixed models that allow for missing data) when all 385 participants who were seen for at least 1 visit were included in the analyses ($P<.001$ for higher PPVT-R and IQ scores over time).

Analysis of those biological and environmental factors associated with neurodevelopmental outcome was consistent with prior studies.[11,36] Increasing years of maternal education and residence in a 2-parent household were both associated with an increase in testing scores with increasing age. Furthermore, we found that the important effect of education could be altered by the addition of special services, suggesting the presence of special services was especially beneficial for children whose mothers had less education. Similar significant findings were noted in the regression analysis model for full-scale IQ and VIQ scores as well as for VIQ z scores, providing additional support for improvement in verbal scores in VLBW children over time.

Although normative data on the PPVT-R indicate a 4.5-point increase in median scores of children tested over time,[27] our participants had a 10- to 11-point increase in scores. Forty-nine percent of children with scores in the mental retardation range at 36 months had scores greater than 70 at 96 months, and more than two thirds of those with borderline scores at 36 months had scores in the normal range at age 8 years. The high rates of morbidity arising from preterm birth result in a large burden on the education services of our country.[37] The societal implications of a 5-point difference in IQ are large.[38] In a population of 100 million, 2.3 million individuals score below 70, a score that in many school districts mandates special-education classes. A shift to the left of the bell-shaped curve for IQ by 5 points increases the number of scores below 70 to 3.6 million. Remedial education in many school districts costs close to an additional $6000 for each student per year. In addition, the label special education carries with it significant individual stigmatization.

Although 20% to 40% of VLBW infants have receptive language delays as toddlers and young children,[39] studies of serial verbal and cognitive testing in VLBW infants are limited, and several reports suggest little change with increasing age.[11,13,32] Our findings differ from these published studies, which may be attributed to several factors. First, both large series include children of higher birth weights and gestational ages than our participants and children were born prior to the years in which our participants were born. This raises the possibility of differences in perinatal intensive care strategies, such as corticosteroid exposure and surfactant administration.[40,41] Neither study followed up the same cohort of children and tested them with the same instrument at each evaluation time. Furthermore, children with significant neurodevelopmental impairments and those residing in adoptive or foster homes were omitted from the one analysis.[11] Additionally, in the other report,[13] only population marginal means derived from multiple linear regression models were given for the 96-month data. Nonetheless, the one study[11] noted that evidence for neonatal white matter injury adversely affected outcome, and early intervention services were found to positively increase testing scores in a subset of children in the other.[13,32] Both are consistent with our findings.

Our study has several methodological strengths. Our VLBW infant cohort was prospectively enrolled and studied longitudinally from the sixth postnatal hour; both serial cranial ultrasonography and later standardized neurodevelopmental assessments were performed. Detailed information was obtained on the prenatal, perinatal, and neonatal course of each child, and demographic data were collected at each follow-up assessment. In addition, the outcome measures were obtained by comprehensive inperson evaluations using standardized assessment tools. Furthermore, no matter whether we selected PPVT-R, IQ, or IQ-associated z scores, all 3 end points led to qualitatively identical results. Although our IQ score results were of only slightly smaller magnitude than the PPVT-R data, they are nevertheless of the same general magnitude and direction. With the VIQ z- score analysis, we obtained statistically significant results that correspond with those observed for the PPVT-R. Finally, our study cohort represents one of the largest and longest followed-up groups of VLBW infants in the postsurfactant era.

Our study also has limitations. Cranial ultrasonography remains the neuroimaging study of choice for screening procedures in VLBW infants but may not be sufficiently sensitive to white matter injury.[42] Our choice of environmental factors was limited to those reported previously in studies of VLBW infants at the time our study began 10 years ago. Other unmeasured and uncontrolled biological or environmental influences may explain our findings. In addition, our study lacked full-term control infants and relied solely on published data for PPVT-R and IQ score comparisons.[35] Our findings of significant increases over time in cognitive functioning are a reflection of the outcome measures used; different measures could lead to different findings. Also, it is well known that the power of statistical interactions generally is

lower than for main effects in regression models. We do not preclude the possibility that nonsignificant interactions in our results may be true or may be due to lack of sufficient power. Finally, as in any study in which more than 1 or 2 a priori specified hypotheses are examined and tested, multiple tests are subject to the multiple-testing problem in which falsely negative results are found to be statistically significant.

In summary, this serial study of verbal and cognitive testing of a large cohort of VLBW infants during early and middle childhood demonstrates significant improvement with increasing CA relative to standard norms with 1 notable exception. Those children with evidence for early-onset IVH followed by later significant CNS injury showed a decline in their scores with increasing age. These data suggest that additional serial studies of cognitive function in VLBW infants with appropriate control-matched participants should be undertaken.

Author Contributions: *Study concept and design:* Ment, Vohr, Duncan, Makuch.
Acquisition of data: Ment, Vohr, Allan, Katz, Schneider, Westerveld, Makuch.
Analysis and interpretation of data: Ment, Vohr, Katz, Westerveld, Duncan, Makuch.
Drafting of the manuscript: Ment, Vohr, Schneider, Duncan, Makuch.
Critical revision of the manuscript for important intellectual content: Vohr, Allan, Katz, Westerveld, Duncan, Makuch.
Statistical expertise: Vohr, Katz, Makuch.
Obtained funding: Ment.
Administrative, technical, or material support: Ment, Allan, Schneider, Duncan, Makuch.
Study supervision: Ment, Schneider, Westerveld, Duncan, Makuch.
Funding/Support: This research was supported by grants NS 27116 of the National Institute of Neurologic Disorders and Stroke and RR 06022 from the National Center of Research Resources.
Acknowledgment: This work benefited greatly from the assistance of the following individuals: Marjorene Ainley, BA, Susan DeLancy, MA, Lisa Perry, MA, from Yale University School of Medicine; Terri Leach, MEd, CAES, Sara Barkett, MA, from Brown University; and Alison Milne, RNC, June Gagnon, MA, from Maine Medical Center.

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